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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FAEGRE & BENSON LLP
PATENT DOCKETING
2200 WELLS FARGO CENTER
90 SOUTH 7TH STREET
MINNEAPOLIS, MN 55402-3901

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,589	GOVINDAN, SERENGULAM V.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-34 and 36-62* is/are pending in the application.

4a) Of the above claim(s) *5-8 and 51-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 9-15, 17-34 and 36-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 05/19/2006 in response to the previous Non-Final Office Action (01/13/2006) is acknowledged and has been entered.

Claims 1-15, 17-34 and 36-62 are currently pending.

Claims 5-8 and 51-62 have been withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-4, 9-15, 17-34 and 36-50 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, the formula shown in claim 32 renders the claim indefinite because the neither the specification or the claims appear to identify what "R" could be.

In response to this rejection, Applicants submit that paragraph 0046 of the present application identifies that "R is the side chain of any amino acid" in the linker.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants argument, the Examiner acknowledges that the specification (paragraph 0046) teaches that "R" can be a side chain of any amino acid. However, it is unclear how this further defines what the R group can be. In other words, the specification does not appear to set forth what constitutes any side chain of any amino acid. As such, one of ordinary skill in the art would not be apprised of the scope of the invention.

New Rejections upon Reconsideration:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-26, 44 and 46-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is apparent that the recited monoclonal antibodies are required to practice the claimed invention, because they are specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cell lines listed in claim 7. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the monoclonal antibodies and they do not appear to be readily available material. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112. While the specification states on page 5 that the cell lines "have been deposited for patent purposes", the specification does not indicate the terms of the deposit.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make

such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 9-15, 17-34 and 36-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 and 47-62 of copending Application No. 11/388,032.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. The conjugate comprising a camptothecin drug and a targeting moiety, wherein the camptothecin drug is linked to the targeting moiety via a cleavable polypeptide and 4-aminobenzyloxy moiety claimed in the conflicting patent application anticipates the currently claimed immunoconjugate comprising an antibody and a chemotherapeutic moiety, wherein the chemotherapeutic drug is linked to the antibody via a linker and a water-solubilizing moiety of the application under examination.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 9, 11-15, 17, 19, 21-24, 27-31, 33-34, 36, 38, 40-43 and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001) in view of Zhao et al. (US 6,716,821, 2004).

Chari et al teach (page 2, lines 11-14 and page 5, lines 30-31) an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4, which binds to the CD19 antigen on B cells, can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers. With regards to the linking group, Chari et al. teach (page 6, lines 1-2) that suitable linking groups include, but are not limited to, esterase labile groups. Moreover, the WO publication teaches (page 6, lines 4-14, page 7, lines 1-5, page 9, formula II and/or III and page 21, lines 28-30) that the linking group is part of a chemical moiety having a peptide such as N-methyl-cysteine or N-methyl-alanine, covalently bound at the C-terminus to an anti-mitotic agent, such as a maytansinoid derivative, via an ester linkage and at the N-terminus to the cell-binding agent, i.e., antibody, via a reactive thiol group, wherein the antibody has been modified with a maleimido group. As a result, the WO publication teaches (page 22, lines 1-2) the conjugates would have 1 to 10 drug molecules per antibody molecule. Moreover, Chari et al. teach (page 30, lines 9-22) that the immunoconjugates may be administered in a suitable form via i.v.. Thus, while Chari et al. do not characterize an antibody specific for an antigen expressed on small cell lung cancer as an antibody specific for an antigen expressed on a carcinoma cell, the claimed functional limitation would be an inherent property because as evidenced by Dictionary.com (see attached), small cell lung cancer is also referred to as small-cell lung carcinoma. Moreover, although Chari et al. does not specifically recite that the immunoconjugate is formulated for parental administration, the claimed functional limitation would be an inherent property because as evidenced by Stedman's Medical Dictionary (see attached), the term parental refers to the introduction of substances to an organism by intravenous, subcutaneous, intramuscular, or intramedullary injection. Thus, the claimed immunoconjugate appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not

possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Chari et al. do not explicitly teach that the linker further comprises a water-solubilizing moiety between the therapeutic moiety and the cell binding agent, wherein the water-solubilizing agent is an aminopolycarboxylate such as PEG. Nor does Chari et al. explicitly teach that the anti-mitotic agent is a taxane, doxorubicin and/or analog thereof, or camptothecin, e.g. CPT, and/or analog thereof.

Zhao et al. teach that cytotoxic conjugates comprising a cytotoxic agent linked to a cell-binding agent via disulfide bonds or short disulfide containing linkers are only sparingly soluble in pharmaceutical solutions typically used for parental administration (column 1, lines 60-65). As a way to circumvent this technical difficulty, Zhao et al. teach cytotoxic agents bearing a polyethylene glycol (PEG) linking group having a terminal active ester and cytotoxic conjugates comprising one or more cytotoxic agents linked to a cell-binding agent via a PEG linking group (column 2, lines 51-57). With regards to the cytotoxic agents, the patent teaches that cytotoxic agents include, but are not limited to, maytansinoids, taxane, daunorubicin analogues and doxorubicin analogues (column 4, lines 1-5). With regards to the cell-biding agents, the patent teaches that cell-binding agents include, but are not limited to, antibodies, interferons, lymphokines, hormones and growth factors (column 64, lines 35-44). Specifically, the patent teaches that the antibodies include, monoclonal antibodies such as My9 and anti-B-4 which binds to a CD19 antigen.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate a water soluble moiety into the immunoconjugate taught by Chari et al in view of the teachings of Zhao et al.. One would have been motivated to do so because Zhao et al. teach that water solubility is one of the many technical difficulties relating to parental administration of cytotoxic conjugates. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating a water soluble moiety into the immunoconjugate taught by Chari et al in view of the teachings of Li et al., one would achieve a way of overcoming poor water solubility and increasing the antibodies efficiency.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute maytansinoids for taxane's and/or doxorubicin as the therapeutic agent of Chari's immunoconjugate. One would have been motivated to do so because each of the agents have been individually taught in the prior art to be therapeutic agents. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have a reasonable expectation of success that by substituting art recognized therapeutic agents such as taxane derivatives and/or doxorubicin analogues for the maytansinoid derivative taught by Chari et al., one would achieve an immunoconjugate effective for the specific delivery and treatment of cancer..

Claims 25 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001) in view of Zhao et al. (US 6,716,821, 2004) in further view of Newton et al. (Blood 2001; 97: 528-535).

Chari et al in view of Zhao et al. teach, as applied to claims 1-4, 9, 11-15, 17, 19, 21-24, 27-31, 33-34, 36, 38, 40-43 and 48-50 above, an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the conjugate comprises a water soluble PEG linking group and the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4 which is a murine IgG1, that binds to the CD19 antigen on B cells can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers.

Chari et al in view of Zhao et al do not explicitly teach that the targeting moiety is the antibody LL2.

Newton et al. teach (abstract) an immunoconjugate comprising LL2 covalently linked to the ribonuclease, onconase, wherein LL2 is an anti-CD22 monoclonal antibody against B-cell lymphoma.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the immunoconjugate as taught by Chari et al. in view of Zhao et al. with a monoclonal LL2 antibody in view of the teachings of Newton et al.. One would have been motivated to do so because as taught by Newton et al., the murine anti-CD22 monoclonal antibody (LL2) was developed for imaging and treatment of non-Hodgkin B-cell lymphomas (NHL). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating LL2 into the immunoconjugate of Chari in view of the teachings of Newton, one would achieve an immunoconjugate which comprises a targeting agent specific for Non-Hodgkin B-cell lymphomas.

Claims 18, 20, 26, 37, 39, 45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (WO 01/24763 A2, 2001) in view of Zhao et al. (US 6,716,821, 2004) and Newton et al. (Blood 2001; 97: 528-535) in further view of Cao et al. (Bioconjugate Chemistry 1998; 9: 635-643).

Chari et al. in view of Zhao et al. and Newton et al. teach, as applied to claims 1-4, 9, 11-15, 17, 19, 21-25, 27-31, 33-34, 36, 38, 40-44 and 48-50 above, an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. Specifically, the combination teaches that the cell binding agent is the monoclonal antibody LL2.

Chari et al. in view of Zhao et al. and Newton et al. do not explicitly teach that the antibody and/or specifically LL2 is multispecific and/or bispecific.

Cao et al. teaches (page 640, 1st column, 2nd full paragraph) that bsMAb's (bispecific monoclonal antibodies) can be used as an effective delivery system for cancer treatment. Specifically, the reference teaches (page 640, 1st column, 3rd full paragraph) that the advantages of using bsMAb to deliver high molecular weight toxins or drugs to tumors, compared to conjugating

such moieties to a Mab, is that chemical conjugations are totally avoided which provides for a more uniform cross-linking between the target and the effector molecule.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a bispecific antibody as the cell-binding agent of the immunoconjugate in view of the teachings of Cao et al.. One would have been motivated to do so because as taught by Cao et al., the advantages of using bsMAb to deliver high molecular weight toxins or drugs to tumors, compared to conjugating such moieties to a Mab, is that chemical conjugations are totally avoided which provides for a more uniform cross-linking between the target and the effector molecule. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using a bispecific antibody as the cell-binding agent of the immunoconjugate taught by Chari et al., one would achieve an immunoconjugate which provides a more uniform cross-linking between the target and the drug molecule.

Claims 1-4, 9-15, 17-24, 27, 29-43, 48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Firestone et al. (US 6,214,345, 2001) in view of Greenwald et al. (US 5,824,701, 1998) and Miller et al. (224th ACS National Meeting, August 18-22, 2002, Boston, Mass., Poster Presentation, *of record*).

Firestone et al. teach a drug ligand conjugate comprising at least one drug molecule, a ligand capable of targeting a selected cell population, and a peptide linker which contains a carboxylic acyl, and a protein peptide specifier, wherein the peptide linker may also contain a self-immolating spacer which spaces the protein peptide sequence and the drug (column 1, lines 28-33). For example, the patent teaches a drug ligand conjugate having the Formula IXb, wherein the antibody is linked to the linker via a thiol, the spacer/peptide linker having a reactive functional group with the free thiol of said antibody, e.g., maleimido group, at its N-terminus and a one or more amino acid residues for linkage to the drug (column 6, lines 62 to 64 and column 7, formula IXb). With regards to the drug, the patent teaches that the drug includes, but is not limited to, doxorubicin, anthracycline antibiotics and taxol (column 2, lines 6-16). With regards to the ligand, the patent teaches that ligands includes any molecule that specifically binds or reactively associates or complexes with a receptor or other receptive moiety associated with a target cell population (column 15, lines 64-67). Specifically, Firestone et al. teach that the ligand is preferably an immunoglobulin which can recognize a tumor-

associated antigen and includes, monoclonal, polyclonal, chimeric and bispecific antibodies, wherein the bispecific antibodies have one arm having specificity for one antigenic site and the other arm recognizes a different target (column 16, line 65 to column 19, line 50). For example, the patent teaches the use of chimeric BR96 for the targeting of drugs to human carcinoma cells with the fucosylated Lewis Y antigen expressed, e.g. ganglioside (column 21, lines 13-21). With regards to the peptide linker, the patent teaches that the peptide linker has an amino acid residue sequence tailored so as to render the peptidyl derivative a selective substrate for drug-activating enzymatic cleavage by a protease, wherein the cleavage removes the peptide linker moiety from the drug conjugate at the tumor site (column 2, lines 23-30). Specifically, the patent teaches that the conjugate is susceptible to enzymatic cleavage at the bond covalently linking the spacer moiety and the protein peptide moiety, wherein the bond may be an ester bond and the ester is formed from the α-carboxylic acid of an amino acid (column 5, lines 5-10 and conjugate of Formula I). With regards to the spacer, the patent teaches a spacer which appears to 100% identical to the claimed linker in claim 32 (column 7, formula IXb). Moreover, the patent teaches that the conjugates are in a form suitable for parenteral administration (column 105, lines 5-8).

Firestone et al. do not explicitly teach that the conjugate further comprises a water-solubilizing moiety.

Greenwald et al. teach that paclitaxel causes hypersensitivity reactions due to its water solubility problems. In order to overcome this problem, Greenwald et al. disclose taxane prodrugs having a water soluble PEG derivative (column 15, line 12 to column 16, line 58).

Miller et al. teach the development of Taxoid derivatives with enhanced toxicity and solubility. Specifically, the poster teaches (2nd column, IV. Attempts to Improve Water Solubility) that one problem associated with antibody-drug conjugate formation is the presence of free drug found in the conjugate as a result of hydrophobic interactions that the cause the drug to "stick" to the antibody such that it compromises the efficiency of the antibody.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the immunoconjugate taught by Firestone et al with the water soluble Taxane PEG prodrug in view of the teachings of Miller et al.. One would have been motivated to do so because as taught by Miller et al., one problem associated with antibody-drug conjugate formation is the presence of free drug found in the conjugate as a result of

hydrophobic interactions that the cause the drug to "stick" to the antibody such that it compromises the efficiency of the antibody. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating a water soluble moiety into the immunoconjugate as taught by Firestone et al., one would achieve a way of overcoming poor water solubility and increasing the drugs efficiency.

Claims 25-26, 44-45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Firestone et al. (US 6,214,345, 2001) in view of Greenwald et al. (US 5,824,701, 1998) and Miller et al. (224th ACS National Meeting, August 18-22, 2002, Boston, Mass., Poster Presentation, *of record*) in further view of Newton et al. (Blood 2001; 97: 528-535).

Firestone et al. in view of Greenwald et al. and Miller et al. teach, as applied to claims 1-4, 9-15, 17-24, 27, 29-43, 48 and 50 above, an immunoconjugate comprising a cell binding agent and at least one therapeutic agent for killing a selected cell population, wherein the conjugate comprises a water soluble PEG linking group and the cell binding agent is a monoclonal antibody or fragment thereof (i.e. Fv, Fab, Fab' and $F(ab')_2$) and the therapeutic agent is an anti-mitotic agent that is linked to the antibody via a linking group. With regards to the antibody, the WO publication teaches (page 17, lines 3-5) that the choice of the appropriate antibody depends on the cell population that is to be targeted. For example, Chari et al. teach (page 17, lines 6-13) that the monoclonal antibody anti-B4 which is a murine IgG1, that binds to the CD19 antigen on B cells can be used to target B cells. Alternatively, the WO publication teaches (page 17, lines 23-31) that antibody or fragment thereof that is specific for lung cancer such as an antibody that binds to an epitope on the CD56 antigen expressed on small cell lung cancers.

Firestone et al. in view of Greenwald et al. and Miller et al. do not explicitly teach that the targeting moiety is the antibody LL2.

Newton et al. teach (abstract) an immunoconjugate comprising LL2 covalently linked to the ribonuclease, onconase, wherein LL2 is an anti-CD22 monoclonal antibody against B-cell lymphoma.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the immunoconjugate as taught by Firestone et al. in view of Greenwald et al. and Miller et al. with a monoclonal LL2 antibody in view of the teachings of

Newton et al.. One would have been motivated to do so because as taught by Newton et al., the murine anti-CD22 monoclonal antibody (LL2) was developed for imaging and treatment of non-Hodgkin B-cell lymphomas (NHL). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by incorporating LL2 into the immunoconjugate of Firestone et al. in view of Greenwald et al. and Miller et al., one would achieve an immunoconjugate which comprises a targeting agent specific for Non-Hodgkin B-cell lymphomas.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

BF
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